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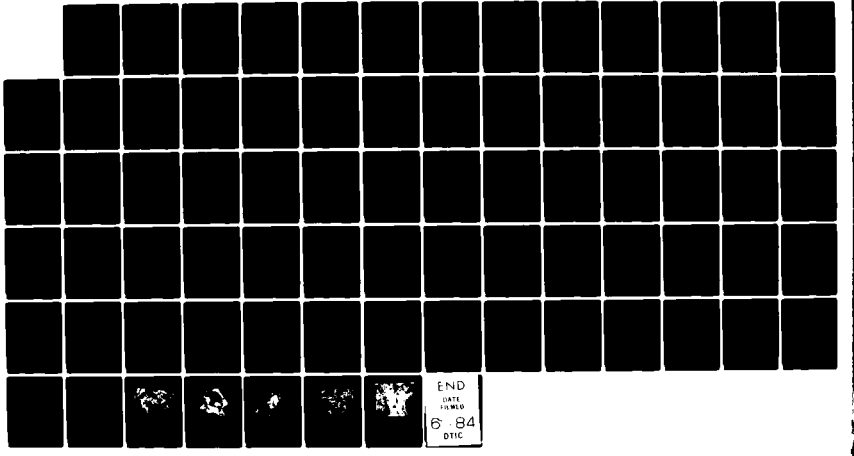

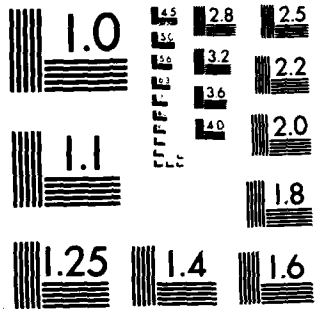

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CHEMOTHERAPY OF RODENT MALARIA

Annual/Final Report

by

WALLACE PETERS MD DSc

September 1981

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US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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1. INTRODUCTION

Although an interim Annual Report was submitted at the beginning of 1981, this is the first full Annual Report submitted by the Principal Investigator from the London School of Hygiene and Tropical Medicine. Unlike the interim report, which covered only the initial four months of the contract, this report summarises the activities of the chemotherapy group for 13 months (12 months initial contract plus one month's extension). The work reported on also includes results obtained from the completion of studies commenced in Liverpool under the contracts held prior to the Principal Investigator's transfer to London.

2. ADMINISTRATIVE EVENTS

The transfer of strains of rodent malaria, referred to in the interim report, has now been completed and facilities for the investigation of the schizontocidal effect of compounds against a wide range of drug-sensitive and resistant strains of rodent malaria now exist at the School's field station at Winches Farm, St. Albans. Close liaison has been maintained by the visits of Colonel Davidson to London and of the PI to WRAIR together with several meetings between Colonel Canfield and the PI coinciding with joint service on the Steering Committee of the WHO CHEMAL Scientific Working Group.

Staff employed on US Army funds are as follows:

Emeritus Professor Dinah James (Pharmacologist)	(part time)
Senior Technologist - Mr B L Robinson (ex-Liverpool)	50% time
Trainee technician - Ms A West.	100% time

Other staff associated with this project but paid from School sources are:

Professor W Peters (PI)	20% time
Dr D C Warhurst (Biologist) (ex-Liverpool)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time.

The conversion of accommodation at Winches Farm is now almost complete and insectary facilities will be available from early in 1982.

The collection of WRAIR compounds transferred from Liverpool has been supplemented by the addition of 33 compounds received from WRAIR for testing in various systems. Much of the work requiring mosquitoes has been held in abeyance pending completion of the new insectaries at Winches Farm but some studies have been undertaken as a result of the high degree of cooperation offered by colleagues in the Ross Institute of the London School and the Muséum Nationale d'Histoire Naturelle in Paris.

3. CHEMOTHERAPY STUDIES

3.1 Causal Prophylaxis

No routine causal prophylaxis tests have been run since

the submission of the interim report. Data on the compounds reported on in that report are included again in this submission and are appended as Tables 2 through 9, and summarised in Table 1.

The 5-phenoxy substituted 8-aminoquinolines WR 231530 and 232584 are both active, the former between 30 and 60 mg/kg sc and po. The latter compound is fully effective between 10 and 30 mg/kg sc and at doses greater than 30 mg/kg p.o. No residual activity (RA) was apparent at these doses. The lepidine WR 237222 is active at 30 mg/kg sc with no RA at that dose level but inactive at 30 mg/kg po. WR 225449, a Mannich base is fully active at 30 mg/kg sc and active at that dose po. RA is marked at 30 mg/kg by either route. The naphthalene methanol WR 232143 is fully active at 10 mg/kg sc with no RA and active at 30 mg/kg po with some RA. WR 218573, 7295 and 181613 display no activity sc and po at 30 mg/kg.

Assessments of residual activity have been performed on all the new WRAIR compounds received and the results of these investigations are summarised and appended as Tables 25, 26. The only compound to show marked residual activity at a dose level of 30 mg/kg sc was the floxacrine analogue WR* (BK 02771) which remained fully effective against P.y.nigeriensis challenge seven days after treatment and was still partially effective, producing delay in the development of infection, 21 days after treatment.

At a dose level of 100 mg/kg sc the Mannich base WR 194965 was fully effective two days post treatment and marked activity was apparent seven days post treatment. Marked residual activity two days after treatment was shown at 100 mg/kg sc by WR 238605 but seven days after treatment no effect remained. The 8-aminoquinoline WR 232584 was also checked for residual activity and the test confirmed that there was no residual activity at the MFAD (30 mg/kg sc) although slight residual activity was present at 100 mg/kg sc.

The 8-aminoquinoline WR 225448 has been examined in the rat model developed by Dr Iréne Landau (see section 3.7) (Table 27) and has shown to have a direct effect on the EE schizont.

3.2 Gametocytocidal action

No routine gametocytocidal screening has been carried out but a number of compounds are scheduled for examination as soon as the Winches Farm insectaries are functioning.

3.3 Blood schizontocides

Data obtained with WRAIR compounds in our blood schizontocidal "four-day test" system with sensitive and drug resistant lines are presented in Tables 11 through 24, and summarised in Table 10. In particular we note that the Mannich base WR 194965 is highly active sc against the N strain and the moderately chloroquine resistant RC strain. The other Mannich base WR 228258 is somewhat less active sc but moreactive po against the N strain and shows a slight but significant loss of activity against the mefloquine resistant N/1100 strain. The 8-aminoquinolines WR 225448, 232584 and 226296 are highly effective against the N strain. While WR 232584 and 225448 are only slightly less active against the primaquine resistant P line, WR 226296

*WR No. requested

is much less effective against this line.

Floxacrine and the two floxacrine analogues WR* (BKO2771) and WR* (BK O2780) have been compared and, whilst both analogues are markedly lessactive than floxacrine, it is interesting to note that all three compounds are more active against the N/1100 line than against N strain and that both floxacrine and WR* (BKO2771) are also significantly more active against NS strain than N strain.

3.4 Sporontocidal action

The absence of suitable insectary facilities has prevented the establishment of a routine screen. However, it has been possible to examine one compound, WR 228258, so far. No sporontocidal action is shown by this compound.

Routine screening for sporontocidal effect is scheduled to begin in early 1982.

3.5 Drug combinations

No studies are currently being made.

3.6 Development and prevention of drug resistance

A long term study is being run of the effects of administering a mixture of mefloquine with "Fansidar" (pyrimethamine + sulfadoxine)* using the relapse technique i.e. fixed, single drug dose at the time of infection. To date, resistance to mefloquine would appear to be inhibited by the simultaneous administration of "Fansidar" when compared with earlier studies on the development of resistance to mefloquine alone. Our initial results are shown graphically in Figure 1 (a) and 1 (b) and would tend to support the claims of Merkli et al (1980) that resistance develops to mefloquine more slowly when it is given together with Fansidar. Further work on this is being carried out and, currently, we are studying the development of mefloquine resistance in a line which is already resistant to Fansidar. No data are as yet available on this line.

3.7 Mode of drug action

The main emphasis of our work on mode of action has been directed towards the two Mannich bases WR 228258 and 194965 and the 8-aminoquinoline WR 225448. The techniques employed so far have been the chloroquine included pigment clumping test (CIPC) and the Desjardin H^3 hypoxanthine incorporation test (HIT). These in vitro techniques utilise P. berghei (CIPC) and the Wellcome-Liverpool strain of P. falciparum (HIT). Additionally, ultrastructural studies on the effects of these compounds in vivo against P. berghei have been undertaken.

(i) P. berghei CIPC

WR 194965 does not induce clumping but will inhibit competitively clumping produced by chloroquine. The dissociation constant (K_i) at the clumping receptor

*WR No. requested

is 80 nmol/l compared to 20 nmol/l for chloroquine and 410 nmol/l for quinine. The slope (n) is 1.7 compared to 2.3 for quinine and 1.0 for mefloquine.
WR 228258 induces pigment clumping which is competitively inhibited by quinine. k_i at the clumping receptor is 372 nmol/l.
WR 225448 neither induces nor inhibits clumping.

(ii) P. falciparum in vitro microtest using Desjardin et al technique of H^3 hypoxanthine incorporation.

WR 194965	IC_{50}	$= < 1.95$ nmol/l	Preliminary results
WR 228258	IC_{50}	$= \sim 1.95$ nmol/l	
WR 225448	IC_{50}	= 252 nmol/l	

(iii) Utrastructural changes

The following is a summary of the main ultrastructural changes in P. berghei blood stages in vivo following administration of 10 mg/kg x 1 sc.

WR 194965 one of the first effects (apparent by 3 hours) is swelling of the digestive vacuoles, and this is followed by the release of some pigment into the cytoplasm. Some mitochondrial swelling occurs..

WR 228258 Although there is some clumping of pigment at high doses, this is not a major feature of the changes in vivo. Digestive vacuoles swell, nuclear blebbing is apparent at 30 minutes and there is general membrane damage.

WR 225448 After 1 to 3 hours, mitochondrial proliferation is found.

(iv) Comments

WR 194965 The activity in the clumping test indicates reaction with the digestive vacuoles (possibly via haemin interactions) and this is confirmed by the electron microscopy results. The k_i for clumping inhibition and the IC_{50} for P. falciparum differ by a factor of 40 which could be accounted for by the short term nature of the CIPC as compared with the prolonged HIT. Also interspecific differences may be involved.

WR 228258 The major observation here is the difference between clumping test results and the results of the P. falciparum study together with the in vivo P.berghei study. The clumping k_m and the incorporation IC_{50} differ by a factor of 186. In addition the studies in vivo showed that clumping was not produced at therapeutic concentrations and that nuclear changes were evident early in the time course.

This indicates that the therapeutic action of the drug depends on a different mode of action from that of chloroquine. The difference between short term P.berghei and long term P.falciparum results in vitro

together with these discrepant in vivo results, suggest that an active metabolite, possibly with anti-nuclear activity, may be involved.

WR 225448 The inactivity in the clumping system and the development of swollen mitochondria followed by mitochondrial proliferation, point to a typical 8-amino-quinoline-like activity. The activity in the long term in vitro test on P.falciparum, although lower (IC_{50} of 252 nmol/l) than that of WR 194965 and 228258, indicates that some production of the active metabolite may be occuring in vitro.

In conclusion, WR 194965 and 228258 appear to have novel modes of action. The apparent anti-nuclear activity of WR 228258 suggests that special attention should be given to its effects on the bone marrow and other actively dividing cells when animal toxity studies are carried out.

WR 225448 has primaquine-like effects and may be expected to have some lytic effects on G6PD deficient erythrocytes. The three drugs may be expected to have activity against chloroquine - resistant malarias.

Electron micrographs illustrating some of the effects of these compounds appear as Plates 1, 2 and 3.

(v) Ultrastructural effects on EE schizonts

Preliminary electron microscope studies on the effects of primaquine and WR 225448 in P.y.nigeriensis sporozoite infected rats have yielded the following results.

1. Primaquine causes thickening and presumably malfunction of mitochondria.

2. WR 225448 produces a primaquine-like effect on mitochondria.

3. WR 225448 also appears to prevent transport of "enzyme-containing lysosomes" from the periphery of the schizont into the host cell.

4. WR 225448 may exert a toxic effect on the hepatocytes themselves.

Some of the effects of a single sc dose of 50 mg/kg of primaquine and 1.0 mg/kg of WR 225448 on the exoerythrocytic schizonts of P.y.nigeriensis are shown in Plates 4 and 5.

3.8 Development of new techniques

The technique for producing high levels of EE schizonts of P.y.nigeriensis developed by Dr. Irene Landau in Paris has been examined and appears to be a very suitable basis for the developmentof a test for true causal prophylactic activity

and also for anti-sporozoite effects of compounds. The commissioning of the new Winches Farm insectaries will allow us to examine this subject in detail and produce a test suitable for routine screening.

A recent visit to the school in London by Dr. Michael Hollingdale drew our attention to the in vitro foetal lung system for the cultivation of rodent malaria. This would appear to hold possibilities for the study of effects of compounds onEE stages in vitro and it is planned to investigate this in more detail.

Preliminary studies on the use of the Duke's mini-feeder have been carried out and we have succeeded in transmitting P.y.nigeriensis to Anopheles stephensi with this equipment. Further studies, including the use of gametocyte producing lines of P.falciparum in culture, are planned.

It is felt that the development of a model for the investigation of the hypnozoite stage, responsible for relapse in P. cynomolgi and, probably also, P. vivax and P. ovale is of great importance and to this end, we intend to examine a number of parasites for suitability.

4.0 PAPERS PUBLISHED

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5. APPENDICES

5.1 Summary of causal prophylactic test data (Table 1)

5.2 Individual causal prophylactic test reports (Tables 2-9)

5.3 Summary of blood schizontocidal (4 day test) data (Table 10)

5.4 Individual blood schizontocidal (4 day test) reports (Tables 11-24)

5.5. Summary of residual activity tests (Tables 25, 26)

5.6 Effects of WR 225448 in rat test for EE activity (Table 27)

5.7 Comparison of development of resistance to mefloquine (alone and administered with Fansidar) in P.berghei (Fig 1a, 1b)

5.8 Electron micrographs showing effects of WR 194965, 228258 and 225448 against blood stages of P.berghei (Plates 1-3)

5.9 Electron micrographs showing effects of primaquine and WR 225448 against EE stages of P.y.nigeriensis (Plates 4,5)

SUMMARY OF CAUSAL PROPHYLACTIC TEST DATA

	WR No.	LIV. No.	Minimum Fully active dose (mg/kg x 1)	Residual action at active dose	COMMENT	Type of Compound
BG 94916	231530AA	1533	30-60 s.c.		Preliminary data	8-aminoquinoline
BG 94916	231530AA	1533	30-60 p.o.		Preliminary data	"
BH 57098	237222AA	1613	> 30 s.c.	Nil at 30	Active at 30 s.c.	"
BH 57098	237222AA	1613	_	-	Inactive at 30 p.o.	"
BH 05361	232584AA	1541	10-30 s.c.	Nil at 30	Fully active at 30 s.c.	"
BH 05361	232584AA	1541	> 30 p.o.	Nil at 30	Active at 30 p.o.	"
BE 66994	218573AA	1543	-	-	Inactive at 30 s.c.	"
BE 66994	218573AA	1543	-	-	Inactive at 30 p.o.	"
BB 49961	7295AD	1556	-	-	Inactive at 30 s.c.	Hydroxyquinoline
BB 49961	7295AD	1556	-	-	Inactive at 30 p.o.	"
BG 62110	181613AB	1557	-	-	Inactive at 30 s.c.	Quinoline Methanol
BG 62110	181613AB	1557	-	-	Inactive at 30 p.o.	"
BG 94925	225449AB	1534	10-30 s.c.	Marked at 30	Fully active at 30 s.c. - all activity residual	Mannich base
BG 94925	225449AB	1534	> 30 p.o.	Marked at 30	Active at 30 p.o. - all activity residual	"
BH 01069	232143AA	1542	3-10 s.c.	Nil at 10	Fully active at 10 s.c.	Naphthalene
BH 01069	232143AA	1542	> 30 p.o.	Present at 30	Active at 30 p.o. - Some residual activity	"

Table 1

CAUSAL PROPHYLAXIS TEST NO: BR 741

DRUG: 8-aminoquinoline LIV/ 1533 WR 231530AA

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION:

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis

DATE:

BOTTLE NO. BG94916

TIME AFTER INFECTION: 2 Hrs.

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	$5/_5$		$5/_5$	5.55		3.67				
30.0	$2/_3$			>8.91						ACTIVE
60.0	$0/_3$			> 14						FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE 30-60 .....mg/kg

RESIDUAL ACTIVITY

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE:

DRUG: 8-aminoquinoline LIV/ 1533 WR 23153OAA BOTTLE NO. BG94916

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES			
	$C^o/_{T^c}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	$5/_5$		$5/_5$	5.55		3.67				
30.0	$2/_3$			>10.39						ACTIVE
60.0	$0/_3$			> 14						FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE.....30-60.....mg/kg

RESIDUAL ACTIVITY

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DATE:

DRUG: 8-aminoquinoline LIV/ 1613 WR 237222AA

BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O

ROUTE OF ADMINISTRATION:

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES			
	$C^o/_{T^c}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5	3/3	5/5	5.55	3.65	3.67				
1.0	3/3			5.34					NIL	INACTIVE
3.0	3/3			5.74					NIL	INACTIVE
10.0	3/3		3/3	5.02		3.73		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 10 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 746

DATE:

DRUG: 8-aminoquinoline LIV/ 1613

WR 237222 AA

BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O

ROUTE OF ADMINISTRATION: sc

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^c}$	XC	C^x/T^x	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	$5/_5$	$3/_3$	$3/_3$	4.89	4.59	4.22				
30.0	$2/_3$		$2/_2$	>8.76		4.12		NIL	>3.87	ACTIVE

MINIMUM FULLY ACTIVE DOSE.....30.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DATE:

DRUG: 8-aminoquinoline$_{LIV/}$ 1613 WR 237222 AA

BOTTLE NO. BH 57098

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION:

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	$5/_5$	$3/_3$	$5/_5$	5.55	3.65	3.67				
3.0	$3/_3$			5.38					NIL	INACTIVE
10.0	$3/_3$			5.53					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.54		3.74		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 720 DATE:

DRUG: 8-aminoquinoline LIV/1541 WR 232584 AA BOTTLE NO. BH 05361

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: sc TIME AFTER INFECTION: 2Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2%P				(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^c}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
Ø	$5/_5$	$3/_3$	$5/_5$	5.57	4.45	4.50				
3.0	$3/_3$			6.17					NIL	
10.0	$1/_3$			>11.27					> 5.70	ACTIVE
30.0	$0/_3$		$3/_3$	>14		4.82		NIL	> 8.43	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE....10-30.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 720 **DATE:**

DRUG: 8-aminoquinoline LIV/ 1541 WR 232584 AA **BOTTLE NO.** BH 05361

PREPARATION: Tween 80/H_2O **ROUTE OF ADMINISTRATION:** po **TIME AFTER INFECTION:** 2 Hrs.

VERTEBRATE HOST: TFW MICE **PARASITE (SUB) SPECIES:** P. y. nigeriensis **STRAIN:** NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	$5/_5$	$3/_3$	$5/_5$	5.57	4.45	4.50				
3.0	$3/_3$			5.80					NIL	INACTIVE
10.0	$3/_3$			5.95					NIL	INACTIVE
30.0	$2/_3$		$3/_3$	>8.53		4.39		NIL	>2.96	ACTIVE

MINIMUM FULLY ACTIVE DOSE.....>30.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE:

DRUG: 8-aminoquinoline LIV/ 1543 WR 218573AA BOTTLE NO. BE66994

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: sc TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	5/5	3/3	5/5	4.94	3.80	3.92				
3.0	3/3			5.03					NIL	INACTIVE
10.0	3/3			5.17					NIL	INACTIVE
30.0	3/3		3/3	5.28		3.87		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE:

DRUG: 8-aminoquinoline LIV/ 1543 WR 218573AA BOTTLE NO. BE66994

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	5/5	3/3	5/5	4.94	3.80	3.92				
3.0	3/3			5.18					NIL	INACTIVE
10.0	3/3			5.25					NIL	INACTIVE
30.0	3/3		3/3	6.19		3.86		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742

DATE:

DRUG: Hydroxyquinoline LIV/ 1556 WR 7295AD **BOTTLE NO.** BB49961

PREPARATION: Tween 80/H_2O **ROUTE OF ADMINISTRATION:** sc **TIME AFTER INFECTION:** 2 Hrs-

VERTEBRATE HOST: TFW MICE **PARASITE (SUB) SPECIES:** P. y. nigeriensis **STRAIN:** NIG

DOSE mg/kg	PATENCY RATE		GMP 2%P				(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	C^x/T^x	f/h	b	c/e	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	5/5	3/3	5/5	5.27	4.00	3.82				
3.0	3/3			5.13					NIL	INACTIVE
10.0	3/3			5.96					NIL	INACTIVE
30.0	3/3			5.13		3.76		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742 DATE:

DRUG: Hydroxyquinoline LIV/ 1556 WR 7295AD BOTTLE NO. BB49961

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			4.73					NIL	INACTIVE
10.0	$3/_3$			4.92					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.49		3.60		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 P.O.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742 DATE:

DRUG: Quinoline Methanol LIV/ 1557 WR 181613 AB BOTTLE NO. BG62110

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: sc TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2&P						(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	C^x/T^x	f/h	b	c/e	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
Ø	$5/_5$	$3/_3$	$5/_5$	5.27	4.00	3.82				
3.0	$3/_3$			5.66					NIL	INACTIVE
10.0	$3/_3$			5.01					NIL	INACTIVE
30.0	$3/_3$		$3/_3$	5.95		3.95		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742 DATE:

DRUG: Quinoline Methanol LIV/ 1557 WR 181613 AB BOTTLE NO. BG 62110

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2%P				(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	$C^o/_{T^o}$	XC	C^x/T^x	f/h	b	c/e	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity		
ø	5/5	3/3	5/5	5.27	4.00	3.82				
3.0	3/3			4.90					NIL	INACTIVE
10.0	3/3			4.59					NIL	INACTIVE
30.0	3/3			5.04		3.70		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE:

DRUG: Mannich Base LIV/ 1534 WR 225449 AB BOTTLE NO. BG 94925

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: sc TIME AFTER INFECTION: 2 Hrs

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2%P				(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	C^x/T^x	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	5/5	3/3	5/5	5.55	3.65	3.67				
3.0	2/3			5.24						
10.0	3/3		3/3	5.09		5.26	$-0.46-\left[\frac{1.65 \times 3.26}{1.67}-1.65\right]$	1.58	NIL	INACTIVE
30.0	0/3		2/3	>14		12.10	$>8.45\ \left[\frac{1.65 \times 10.10}{1.67}-1.65\right]$	8.34	NIL	FULLY ACTIVE-ALL ACTIVITY RESIDUAL

MINIMUM FULLY ACTIVE DOSE.....10-30.....mg/kg

RESIDUAL ACTIVITY MARKED AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 8a

CAUSAL PROPHYLAXIS TEST NO: BR 741 DATE:

DRUG: Mannich Base LIV/ 1534 WR 225449 AB BOTTLE NO. BG94925

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE GMP 2%P						(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	$5/_5$	$3/_3$	$5/_5$	5.55	3.65	3.67				
10.0	$3/_3$		$3/_3$	6.42		3.79	0.87 -	NIL	0.87	INACTIVE
30.0	$3/_3$		$3/_3$	10.75		8.82	$5.20 - \left[\frac{1.65 \times 6.82}{1.67} - 1.65\right]$	5.09	0.11	RESIDUAL ACTIVITY ONLY

MINIMUM FULLY ACTIVE DOSE.....>30.....mg/kg

RESIDUAL ACTIVITY MARKED AT 30 mg/kg x 1 p.o. PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728

DATE:

DRUG: Naphthalene LIV/ 1542 WR 232143AA

BOTTLE NO. BH 01069

PREPARATION: Tween 80/H_2O

ROUTE OF ADMINISTRATION: sc

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
ø	$5/_5$		$5/_5$	4.94	3.80	3.92				
3.0	$2/_3$			>8.01		3.86		NIL	>3.07	SLIGHTLY ACTIVE
10.0	$0/_3$			>14		4.65		NIL	>9.06	FULLY ACTIVE
30.0	$0/_3$			>14		8.76	$>9.06-\left[\frac{1.80 \times >6.76}{1.92}-1.80\right]$	>4.54	>7.36	FULLY ACTIVE-SOME RESIDUAL ACTIVITY

MINIMUM FULLY ACTIVE DOSE.....3-10.....mg/kg

RESIDUAL ACTIVITY NIL AT 10 mg/kg x 1 s.c.
PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728 DATE:

DRUG: Naphthalene LIV/ 1542 WR 232143AA BOTTLE NO. BH 01069

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: po TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)\frac{(b-a)(e-a)}{(c-a)}-(b-a)$	Residual Activity	Prophylactic Activity	COMMENT
Ø	$5/_5$	$3/_3$	$5/_5$	4.94	3.80	3.92				
3.0	$3/_3$			5.38		3.83		NIL	NIL	
10.0	$2/_3$			>8.08		3.96		NIL	>3.14	SLIGHTLY ACTIVE
30.0	$1/_3$		$3/_3$	>11.00		7.65	$>6.06-\left[\frac{1.80\times5.65}{1.92}-1.80\right]$	3.50	>2.56	ACTIVE-SOME RESIDUAL ACTIVITY

MINIMUM FULLY ACTIVE DOSE.....>30.....mg/kg

RESIDUAL ACTIVITY PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA

L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED 50	ED 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90
1541	WR 232584 BH 05361	sc	0.3	0.5	1.9	3.8	0.4	0.8	2.1	4.2								
		po	0.4	0.6	3.2	5.3	0.9	1.5	2.6	4.3								
1391	WR 226296 BG 44452	sc	0.5	1.2	1.9	1.6	0.6	0.5	26.0	21.7								
		po	0.3	0.5	2.9	5.8	0.7	1.4	7.8	15.6								
LON No.																		
1707	WR 194965AG BG 56327	sc	2.2	3.8	4.2	1.1	>MTD	-										
1708	WR 228258AH BJ 30663	sc	4.0	10.0													26.0	2.6
		po	1.2	2.4													18.0	7.9
1709	WR 225448AG BH 58522	sc	0.2	0.3	0.8	2.7	0.4	1.3	1.2	4.0							0.4	1.3
		po	0.1	0.2	0.6	3.0	0.6	3.0	1.2	6.0								

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA

LON/ L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED 50	ED 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90
LIV 1307	WR 182232AC	sc	3.2	7.3														
	BE 08456	po	4.2	7.8														
LIV 1354	WR 194343	sc	1.5	4.2														
	BC 06452	po	3.9	7.6														
LIV 1381	WR 215295	sc	4.6	11.0														
LON 1722	BE 16378	po	5.6	11.7														
LIV 1382	WR 216100	sc	2.1	5.6														
	BE 17491	po	2.6	6.1														
LIV 1542	WR 232143	sc	16.5	50.0														
	BH 01069																	
LIV 1528	Floxacrine	SC	0.7	3.0	0.8	0.3											1.3	0.4
LON 1752	BK 02771	sc	3.0	84.0	25.0	0.3											46.0	0.5

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA

L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED 50	ED 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90
LON 1753	BKO2780	sc	41.5	>100	>100												48.0	<0.5
LON 1718	WR 158124 BD 22997	sc	13.5	42.0														

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 11a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 232584 BHO5361 LIV/1541 ..... PARASITE (SUB) SPECIES..P.b.berghei.....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.3	5		-	53.5 ± 5.0
	1.0	5			0
	3.0	5	1	-	0
	10.0	5		-	0
	ø	10		42.6	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	78.7 ± 2.8
	1.0	5		-	67.1 ± 2.4
	3.0	5	1	-	2.1 ± 1.2
	10.0	5		-	0
	ø	10		48.3	
ED_{50} (range)	0.8(0.5-1.4)				
ED_{90} (range)	1.9(1.1-3.2)				
	Resistance factor 90 3.8				

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

DATE.....5th January 1982..... PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 11b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 BH 05361 LIV/1541 ..... PARASITE (SUB) SPECIES. P.b.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 100
RC	0.3	5		-	17.2 ± 11.0
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	ø	10		3.5	
ED_{50} (range)	0.2(0.1-0.3)				
ED_{90} (range)	0.4(0.3-0.5)				
	Resistance Factor 90 0.8				
P	0.3	5		-	67.2 ± 4.1
	1.0	5		-	61.3 ± 5.7
	3.0	5	1	-	28.1 ± 5.7
	10.0	5		-	0
	ø	10		23.5	
ED_{50} (range)	1.0(0.4-2.2)				
ED_{90} (range)	2.1(0.7-4.7)				
	Resistance factor$_{90}$ 4.2				

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DATE 5th January 1962 PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 11c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 / BH 05361 / LIV/1541 ..... PARASITE (SUB) SPECIES..P.b.berghei.....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.3	5		-	71.8 ± 3.6
	1.0	5		-	1.9 ± 0.9
	3.0	5	1	-	0
	10.0	5		-	0
	ø	10		42.6	
ED_{50} (range)	0.4(0.3-0.4)				
ED_{90} (range)	0.6(0.5-0.8)				
	Resistance factor 90 1.0				
	0.3	5		-	76.6 ± 2.0
	1.0	5		-	75.0 ± 4.4
	3.0	5	1	-	46.8 ± 7.6
	10.0	5		-	0
	ø	10		48.3	
ED_{50} (range)	1.9(1.1-3.0)				
ED_{90} (range)	3.2(1.9-5.1)				
	Resistance factor 90 5.3				

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

DATE 5th January 1982 PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 11d

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 / BH 05361 / LIV/1541 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.3	5		-	51.4 ± 16.5
	1.0	5		-	40.0 ± 16.5
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.5(0.2-1.0)				
ED_{90} (range)	0.9(0.5-1.8)				
	Resistance factor 90 1.5				
P	0.3	5		-	78.3 ± 2.5
	1.0	5		-	66.4 ± 5.7
	3.0	5	1	-	51.1 ± 3.3
	10.0	5		-	0
	Ø	10		23.5	
ED_{50} (range)	1.3(0.5-3.3)				
ED_{90} (range)	2.6(0.9-6.2)				
	Resistance factor 90 4.3				

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

DATE 5th January 1982 PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 12a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 BH 44452 LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.3	5		-	69.0 ± 2.7
	1.0	5		-	4.2 ± 1.8
	3.0	5	1	-	2.1 ± 0.9
	10.0	5		-	0
	Ø	10		42.6	
ED_{50} (range)	0.5(0.2-0.6)				
ED_{90} (range)	1.2(0.6-1.8)				
	Resistance factor 90 1.0				
NS	0.3	5		-	71.2 ± 2.8
	1.0	5		-	66.3 ± 3.6
	3.0	5	1	-	15.3 ± 5.6
	10.0	5		-	
	Ø	10		48.3	
ED_{50} (range)	0.8(0.4-1.7)				
ED_{90} (range)	1.9(1.0-4.0)				
	Resistance factor 90 1.6				

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DATE 5th January 198 2 PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 12b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 BH 44452 LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 10$
RC	0.3	5		-	91.4 ± 27.4
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.4(0.3 -0.7)				
ED_{90} (range)	0.6(0.4-0.9)				
	Resistance factor $_{90}$ 0.5				
P	0.3	5		-	95.3 ± 4.9
	1.0	5		-	87.7 ± 3.3
	3.0	5	1	-	75.8 ± 7.4
	10.0	5		-	32.3 ± 6.5
	Ø	10		23.5	
ED_{50} (range)	4.6(1.8-10.0)				
ED_{90} (range)	26 (10-56)				
	Resistance factor $_{90}$ 21.7				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 12c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 226296 / BH 44452 / LIV/1391 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 10$
N	0.3	5		-	54.5 + 7.8
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		48.3	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	73.7 ± 2.4
	1.0	5		-	72.1 ± 3.2
	3.0	5	1	-	19.5 ± 5.2
	10.0	5		-	0
	Ø	10		48.3	
ED_{50} (range)	1.6(1.2-2.2)				
ED_{90} (range)	2.9(2.2-4.0)				
	Resistance factor 90 5.8				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 12d

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 226296 BH 44452 LIV/1391 PARASITE (SUB) SPECIES.. P. b. berghei

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.3	5		-	34.3 ± 11.0
	1.0	5		-	11.4 ± 5.5
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED_{50} (range)	0.3(0.2-0.6)				
ED_{90} (range)	0.7(0.4-1.2)				
	Resistance factor 90 1.4				
P	0.3	5		-	61.3 ± 7.4
	1.0	5		-	58.7 + 2.5
	3.0	5	1	-	51.9 ± 4.1
	10.0	5		-	8.5 ± 3.3
	Ø	10		23.5	
ED_{50} (range)	1.4(0.4-3.8)				
ED_{90} (range)	7.8(2.0-22.0)				
	Resistance factor 90 15.6				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 13a

COMPOUND NAME or NUMBER: WR 194965 AG, BG 56327, LON 1707 (BLOOD SCHIZONTOCIDES)

PARASITE (SUB) SPECIES: P.berghei

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	1.0	5		-	95.0 ± 3.0
	3.0	5		-	39.0 ± 6.2
	10.0	5	1	-	0
	ø	10		53.0	
ED_{50} (range)	2.2(1.8-2.8)				
ED_{90} (range)	3.8(3.1-4.7)				
	Resistance factor $_{90}$ 1.0				
NS	1.0	5		-	98.0 ± 3.6
	3.0	5		-	40.0 ± 5.6
	10.0	5	1	-	0.05 ± 0.05
	30.0	5		-	0
	ø	10		46.0	
ED_{50} (range)	2.4(1.9-3.0)				
ED_{90} (range)	4.2(3.2-5.0)				
	Resistance factor $_{90}$ 1.1				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 13b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 194965 BG 56327 LON 1707 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 10$
RC	3.0	5		-	98.5 ± 4.5
	10.0	5		-	95.0 ± 3.2
	30.0	5	1	-	84.0 ± 4.3
	100.0	5		-	> LD 100
	Ø	10		6.2	
ED_{50} (range)	> MTD				
ED_{90} (range)	≫ MTD				
	Resistance factor $_{90}$				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor $_{90}$				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 14a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 228258 / BJ 30663 / LON 1708 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	1.0	5		-	95.3 ± 5.9
	3.0	5		-	83.6 ± 7.7
	10.0	5	1	-	7.8 ± 3.6
	30.0	5		-	0.2 ± 0.1
	ø	10		37.6	
ED_{50} (range)	4.0(2.6-6.7)				
ED_{90} (range)	10.0 (7.0-17.0)				
	Resistance factor $_{90}^{50}$ 1.0				
N/1100	1.0	5		-	85.0 ± 10.0
	3.0	5		-	51.3 ± 15.9
	10.0	5	2	-	39.0 ± 5.2
	30.0	10		-	33.1 ± 5.4
	100.0	5		-	0
	ø	10		17.7	
ED_{50} (range)	13.0(7.5-23.0)				
ED_{90} (range)	26.0(15.0-44.0)				
	Resistance factor $_{90}$ 2.6				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 14b

COMPOUND NAME or NUMBER: WR 228258AH / BJ 30663 / LON 1708 (BLOOD SCHIZONTOCIDES)

PARASITE (SUB) SPECIES: P.berghei

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 10$
N	1.0	5		-	54.0 ± 15.0
	3.0	5		-	15.4 ± 11.2
	10.0	5	1	-	0
	Ø	10		37.6	
ED_{50} (range)	1.2(0.9-1.7)				
ED_{90} (range)	2.4(1.0-3.4)				
	Resistance factor 90 1.0				
N/1100	1.0	5		-	88.4 ± 7.2
	3.0	5		-	56.3 ± 6.9
	10.0	5	2	-	49.1 ± 11.4
	30.0	10		-	27.9 ± 9.0
	100.0	5		-	0
	Ø	10		17.7	
ED_{50} (range)	9.5(4.4-24.0)				
ED_{90} (range)	18.0(8.0-40.0)				
	Resistance factor 90 7.9				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 15a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 22448AG / BH 58522 / LON 1709 .....

PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.1	5		-	87.5 ± 5.2
	0.3	5		-	4.5 ± 1.0
	1.0	5	1	-	0
	3.0	5		-	0
	ø	10		42.5	
ED_{50} (range)	0.2(0.1-0.2)				
ED_{90} (range)	0.3(0.2-0.3)				
	Resistance factor $_{90}$ 1.0				
NS	0.1	5		-	96.5 ± 8.5
	0.3	5		-	87.8 ± 4.8
	1.0	5	1	-	5.1 ± 2.3
	3.0	5		-	0
	ø	10		57.4	
ED_{50} (range)	0.4(0.2-0.6)				
ED_{90} (range)	0.8(0.3-1.1)				
	Resistance factor $_{90}$ 2.7				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 15b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448AG / BH 58522 / LON 1709 ..... PARASITE (SUB) SPECIES... P.berghei .....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
RC	0.1	5		-	98.1 ± 7.5
	0.3	5		-	60.0 ± 8.4
	1.0	5	1	-	0
	3.0	5		-	0
	Ø	10		4.1	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.4(0.3-0.6)				
	Resistance factor $_{190}$ 1.3				
P	0.1	5		-	82.7 ± 6.5
	0.3	5		-	66.4 ± 12.0
	1.0	5	1	-	21.2 ± 4.6
	3.0	5		-	1.3 ± 0.4
	Ø	10		20.8	
ED_{50} (range)	0.3(0.2-0.7)				
ED_{90} (range)	1.2(0.8-2.4)				
	Resistance factor $_{190}$ 4.0				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 15c

COMPOUND NAME or NUMBER: WR 225448 AG, BH 58522, LON 1709 (BLOOD SCHIZONTOCIDES)

PARASITE (SUB) SPECIES: P.berghei

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N/1100	0.1	5		-	68.0 ± 7.7
	0.3	5		-	48.1 ± 13.1
	1.0	5	1	-	0.1 ± 0.1
	3.0	5		-	0
	ø	10		23.0	
ED_{50} (range)	0.2(0.1-0.4)				
ED_{90} (range)	0.4(0.2-0.7)				
	Resistance factor $_{190}$ 1.3				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor $_{190}$				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 15d

WR 225448 AG (BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER BH 58522 LON 1709 PARASITE (SUB) SPECIES.. P. berghei

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	01	5		-	65.5 ± 19.2
	0.3	5		-	2.9 ± 0.8
	1.0	5	1	-	0.01 ± 0.01
	3.0	5		-	0
	Ø	10		42.5	
ED_{50} (range)	0.1(0.1-0.2)				
ED_{90} (range)	0.2(0.2-0.3)				
	Resistance factors I 90 1.0				
NS	0.1	5		-	89 .9 ± 4.2
	0.3	5		-	69.0 ± 4.7
	1.0	5	1	-	1.1 ± 0.4
	3.0	5		-	0
	Ø	10		57.4	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.6(0.4-1.0)				
	Resistance factor I 90 3.0				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 15e

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 225448AG / BH 58522 / LON 1709 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.1	5		-	96.6 ± 8.0
	0.3	5		-	60.0 ± 10.8
	1.0	5	1	-	0.7 ± 0.5
	3.0	5		-	0
	ø	10		4.1	
ED_{50} (range)	0.3(0.2-0.4)				
ED_{90} (range)	0.6(0.4-0.8)				
	Resistance factor I90 3.0				
P	0.1	5		-	79.8 ± 10.0
	0.3	5		-	51.9 ± 11.1
	1.0	5	1	-	22.1 ± 2.8
	3.0	5		-	1.0 ± 0.4
	ø	10		20.8	
ED_{50} (range)	0.3(0.2-0.5)				
ED_{90} (range)	1.2(0.6-1.9)				
	Resistance factor I90 6.0				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 16a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 182232 AC, BE 08456, LIV/1307 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	3.0	5		-	59.8 ± 17.5
	10.0	5		-	1.1 ± 0.4
	30.0	5	1	-	0.08 ± 0.04
	100.0	5		-	0
	Ø	10		26.4	
ED_{50} (range)	3.2(1.8-6.0)				
ED_{90} (range)	7.3(4.3-14.5)				
	Resistance factor I90				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 16b

WR 182232 AC
BE 08456
COMPOUND NAME LIV/1307 (BLOOD SCHIZONTOCIDES)
or NUMBER ..... PARASITE (SUB) SPECIES P.berghei .....

FORMULATION_ Tween 80/H_2O Route of administration : po

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10
N	3.0	5		-	60.9 ± 5.2
	10.0	5		-	8.0 ± 3.5
	30.0	5	1	-	0
	100.0	5		-	0
	Ø	10		17.4	
ED_{50} (range)	4.2(3.1-5.4)				
ED_{90} (range)	7.8(5.8-10.2)				
	Resistance factor I90				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor I90				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 17a

WR 194343 (BLOOD SCHIZONTOCIDES)
BC 06452
COMPOUND NAME LIV/1354
or NUMBER ..... PARASITE (SUB) SPECIES P.berghei .....

FORMULATION Tween 80/H_2O Route of administration : SC

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 100
N	3.0	5		-	20.5 ± 4.7
	10.0	5		-	0.8 ± 0.7
	30.0	5	1	-	0
	100.0	5		-	0
	Ø	10		26.4	
ED_{50} (range)	1.5(1.1-2.4)				
ED_{90} (range)	4.2(2.3-5.3)				
	Resistance factor I90				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 17b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 194343 BC 06452 LIV/1354 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : po

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10
N	1.0	5		-	83.6 ± 4.0
	3.0	5		-	69.9 ± 4.2
	10.0	5	1	-	15.5 ± 1.8
	30.0	5		-	0
	Ø	10		17.4	
ED_{50} (range)	3.9(1.6-6.2)				
ED_{90} (range)	7.6(3.2-12.2)				
	Resistance factor I90				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 18a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 215295 / BE 16378 / LIV/1381/LON 1722 ..... PARASITE (SUB) SPECIES..... P.berghei.....

Route of administration : sc

FORMULATION Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	3.0	5		-	69.7 ± 2.9
	10.0	5		-	21.9 ± 5.1
	30.0	5	1	-	0.2 ± 0.1
	100.0	5		-	0
	Ø	10		26.4	
ED_{50} (range)	4.6(3.4-7.2)	100 = [illegible] LD_{40}			
ED_{90} (range)	11.0(8.0-17.0)				
	Resistance ~~factor~~ 190				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 18b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 215295 / BE 16378 / LIV/1381/LON 1722 ... PARASITE (SUB) SPECIES ..... P.berghei .....

Route of administration : po

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	3.0	5		-	76.6 ± 2.3
	10.0	5		-	31.3 ± 5.7
	30.0	5	1	-	0.2 ± 0.2
	100.0	5		-	0
	Ø	10		17.4	
ED_{50} (range)	5.6(3.8-8.6)				
ED_{90} (range)	11.7(8.0-18.2)				
	Resistance factor 190				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 19a

WR 216100 (BLOOD SCHIZONTOCIDES)
BE 17491
COMPOUND NAME LIV/1382
or NUMBER ..... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 100
N	3.0	5		-	33.3 $\pm$ 12.4
	10.0	5		-	2.2 $\pm$ 1.5
	30.0	5	1	-	0
	100.0	5		-	0
	ø	10		26.4	
ED_{50} (range)	2.1(1.5-3.0)				
ED_{90} (range)	5.6(4.2-8.0)				
	Resistance factor 190				
ED_{50} (Range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 19b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 216100 BE 17491 LIV/1382 PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : po

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 100
N	1.0	5		-	72.8 ± 4.7
	3.0	5		-	57.8 ± 2.8
	10.0	5	1	-	12.2 ± 6.6
	30.0	5		-	0.01 ± 0.01
	Ø	10		17.4	
ED_{50} (range)	2.6(1.4-5.4)				
ED_{90} (range)	6.1(3.4-12.8)				
	Resistance factor 190				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 20

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232143 BH 01069 LIV/1542 ..... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	3.0	5		-	88.6 ± 9.7
	10.0	5		-	84.1 ± 6.8
	30.0	5	1	-	43.2 ± 13.8
	100.0	5		-	0.5
	ø	10		26.4	
ED_{50} (range)	16.5(6.0-39.0)	100 = ∿ LD_{40}			
ED_{90} (range)	50.0(18-120)				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 21a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER .Floxacrine..... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO ~ D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	0.1	5		-	85.8 ± 6.1
	0.3	5		-	76.2 ± 2.1
	1.0	5	1	-	63.5 ± 3.7
	3.0	5		-	6.2 ± 2.1
	Ø	10		11.0	
ED_{50} (range)	0.7(0.2-1.6)				
ED_{90} (range)	3.0(1.2-7.4)				
	Resistance factor f90 1.0				
NS	0.1	5		-	54.9 ± 3.4
	0.3	5		-	42.5 ± 11.0
	1.0	5	1	-	12.4 ± 8.8
	3.0	5		-	1.8 ± 0.9
	Ø	10		11.3	
ED_{50} (range)	0.2(0.1-0.3)				
ED_{90} (range)	0.8(0.5-1.7)				
	Resistance factor I90 0.3				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 21b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER Floxacrine ..... PARASITE (SUB) SPECIES P.berghei .....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 100
N/1100	0.1	5		-	100 ± 1.6
	0.3	5		-	52.9 ± 8.6
	1.0	5	1	-	19.5 ± 5.9
	3.0	5		-	4.9 ± 2.3
	ø	10		8.5	
ED_{50} (range)	0.7 (0.2-1.4)				
ED_{90} (range)	1.3(0.5-2.8)				
	Resistance factor 190 0.4				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 22a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: BK 02771 LON/1752 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10(
N	0.1	5	-	-	85.5 ± 5.6
	0.3	5	-	-	77.5 ± 3.0
	1.0	5	1	-	67.3 ± 5.4
	3.0	5	-	-	59.1 ± 5.8
	10.0	5	-	-	34.5 ± 8.0
	Ø	10	-	11.0	
ED_{50} (range)	3.0(0.9- 8.0)	Interpolated graphically			
ED_{90} (range)	84.0(24 - >100)				
	Resistance factor I90 1.0				
NS	0.1	5		-	66.4 ± 5.2
	0.3	5*		-	62.5 ±
	1.0	5	1	-	57.3 ± 2.5
	3.0	5		-	50.8 ± 4.8
	10.0	5		-	17.2 ± 3.4
	Ø	10		11.3	
ED_{50} (range)	1.0(0.2-4.0)	*2/5 died			
ED_{90} (range)	25.0(5.0-100)				
	Resistor factor I90 0.3				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 22b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: BKO2771 LON/1752 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10(
N/1100	0.1	5		-	87.1 ± 5.4
	0.3	5		-	72.5 ± 6.1
	1.0	5	1	-	60.7 ± 12.6
	3.0	5		-	47.5 ± 4.3
	10.0	5		-	25.4 ± 4.3
	ø	10		8.5	
ED_{50} (range)	1.8(0.9-4.6)				
ED_{90} (range)	46.0(21 - >100)				
	Resistance factor I90 0.5				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 23a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: BK 02780 LON/1753 ..... PARASITE (SUB) SPECIES: P.berghei .....

FORMULATION: Tween 80/H_2O Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% / Control PR% x 10
N	0.1	5		-	84.0 ± 3.1
	0.3	5		-	76.4 ± 1.0
	1.0	5	1	-	66.4 ± 3.5
	3.0	5		-	61.1 ± 4.4
	10.0	5		-	55.8 ± 5.2
	ø	10		11.0	
ED_{50} (range)	41.5(4.4-90)				
ED_{90} (range)	> 100				
	Resistance factor 190				
NS	0.1	5		-	74.2 ± 3.9
	0.3	5		-	70.4 ± 4.2
	1.0	5	1	-	63.4 ± 4.4
	3.0	5		-	53.3 ± 2.4
	10.0	5		-	47.6 ± 2.4
	ø	10		11.3	
ED_{50} (range)	22.0(9.0-60)				
ED_{90} (range)	> 100				
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 23b

(BLOOD SCHIZONTOCIDES)

BK 02780
LON/1753

COMPOUND NAME or NUMBER ..... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10
N/1100	0.1	5		-	98.8 ± 3.8
	0.3	5		-	83.5 ± 6.9
	1.0	5	1	-	65.4 ± 5.7
	3.0	5		-	56.2 ± 9.9
	10.0	5		-	51.1 ± 9.0
	ø	10		8.5	
ED_{50} (range)	3.5(1.3-16)				
ED_{90} (range)	48(18 - 100)				
	Resistance factor I90 36.9				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 23b

(BLOOD SCHIZONTOCIDES)

BK 02780
LON/1753

COMPOUND NAME or NUMBER ..... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10
N/1100	0.1	5		-	98.8 ± 3.8
	0.3	5		-	83.5 ± 6.9
	1.0	5	1	-	65.4 ± 5.7
	3.0	5		-	56.2 ± 9.9
	10.0	5		-	51.1 ± 9.0
	ø	10		8.5	
ED_{50} (range)	3.5(1.3-16)				
ED_{90} (range)	48(18 - 100)				
	Resistance factor I90 36.9				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST TABLE 24

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 158124 / BD 22997 / LON/1718 ..... PARASITE (SUB) SPECIES: P.berghei .....

Route of administration : sc

FORMULATION: Tween 80/H_2O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}}$ x 10
N	3.0	5		-	90.9 ± 9.0
	10.0	5		-	78.0 ± 11.9
	30.0	5	1	-	18.2 ± 6.5
	100.0	5		-	1.4 ± 0.7
	Ø	10		26.4	
ED_{50} (range)	13.5(7.0-34)				
ED_{90} (range)	42.0(22 - 110)				
	Resistance factor 190				
ED_{50} (range)					
ED_{90} (range)					
	Resistor factor 190				

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SUMMARY OF RESIDUAL ACTIVITY TESTS TABLE 25

Dose = 30 mg/kg s.c. x 1

RESIDUAL ACTIVITY AT D+

LON	BN	WR No.	MFED	2	7	14	Type of Compound
1707	BG56327	194965 AG		±			Mannich base
1708	BJ30663	228258 AH		-			Mannich base
1709	BH58522	225448 AG		-			8-aminoquinoline
1715	AG99266	5990	30-60	-			8-aminoquinoline
1716	AJ63248	9792		-			
1717	AB65541	61112		-			Hydroxypyridine
1718	BD22997	158124		-			
1719	BE50003	181023	30-100	-			4-methyl primaquine
1720	BE17580	182234	3-10	-			2-methyl primaquine
1721	ZP12775	211814	1-3	-			8-aminoquinoline
1722	ZN43444	215295	300	-			8-aminoquinoline
1723	ZN81499	228000	10.30	-			8-aminoquinoline
1724	ZN78910	228583	30	-			8-aminoquinoline
1725	BH13989	233627		-			8-aminoquinoline
1726	BH35770	235485		-			8-aminoquinoline
1727	BH69990	238605		+			
1728	BJ08189	243789		-			
1729	BJ45691	246315		+			
1730	BJ51779	247705		±			
1731	BJ59202	248412		+ -			
1732	BH58120	237375		-			
1733	BG66798	228708	10-30	±			8-aminoquinoline
1734	BH89438	242511		+ -			
1736	BJ78592			-			
1740	AY29540			+			Quinolone/Naphthoquinone
1741	BC78878			+			
1751	ZN41968			-			
1752	BK02771			+++	++	+	Floxacrine analogue
1753	BK02780			-			Floxacrine analogue

± Residual Activity - No Residual Activity

\+ Slight Residual Activity

++ Marked Residual Activity

+++ Fully Residual Activity

TABLE 26

SUMMARY OF RESIDUAL ACTIVITY TEST

Dose = 100 mg/kg sc

				RESIDUAL ACTIVITY AT D+			
LON	BN	WR No.	MFED	2	7	14	Type of Compound
1707	BG56327	194965 AG		++	++		Mannich base
1727	BH69990	238605		++	-		
1729	BJ45691	246315		++***	-**		
1730	BJ51779	247705		MTD	MTD		
1731	BJ59202	248412		+*	-		
1734	BH89438	242511		++**	-***		
1740	AY29540			+	-		Quinoline/Naphthoquinone
1741	BC78878			+	-		

* 2/5 DIED

** 3/5 DIED

*** 4/5 DIED

SUMMARY OF RESULTS OF RAT TEST FOR ACTIVITY AGAINST

EXOERYTHROCYTIC STAGES

COMPOUND : WR225448 (Lon 1709) ROUTE : sc x 1

VERTEBRATE HOST: Albino rats (body weight = 60g)

INVERTEBRATE HOST: A.stephensi (50-100 mosquitoes/rat)

PARASITE: P.y.nigeriensis

TREATED: 1 hour post infection

Dose	Schizonts in biopsy at + 45 hours	Blood films				
mg/kg		D+3	D+4	D+6	D+8	D+9
Ø	10-20/section. all large	+				+
0.25	13-18/section. Variable in size	+			+	
1.0	0-24 /section. Very variable in size	+			-	
3.0	0-1/section. Very small, abnormal	-	-	+		+
5.0	0 seen	-	-	+	+	
10.0	0 seen	-	-	-	-	-
30.0	0 seen	-	-	-	-	-

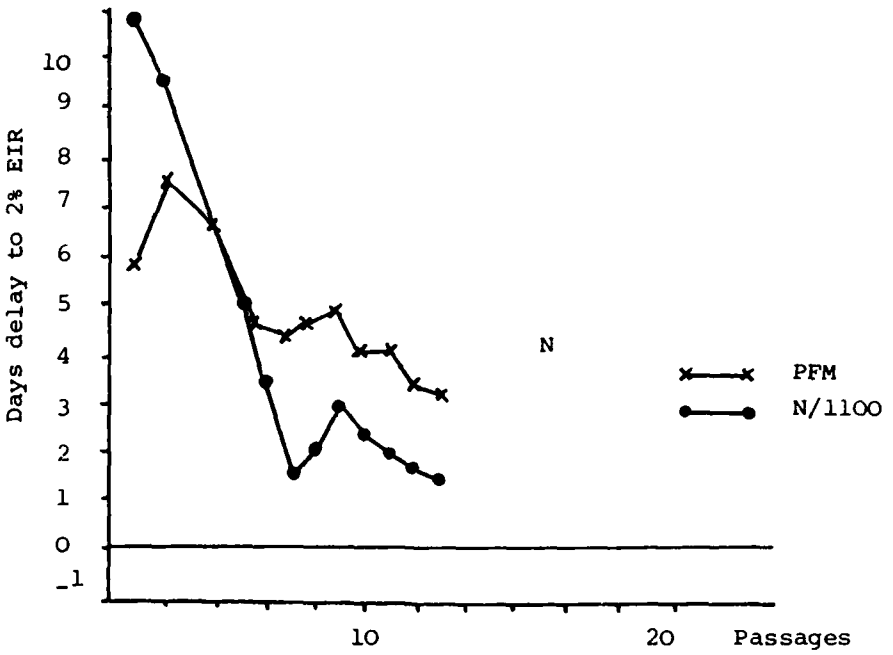

Fig. 1a. Development of resistance in drug sensitive P.berghei (N strain) to mefloquine alone (N/1100) and mefloquine administered together Fansidar (PFM) using the relapse technique.

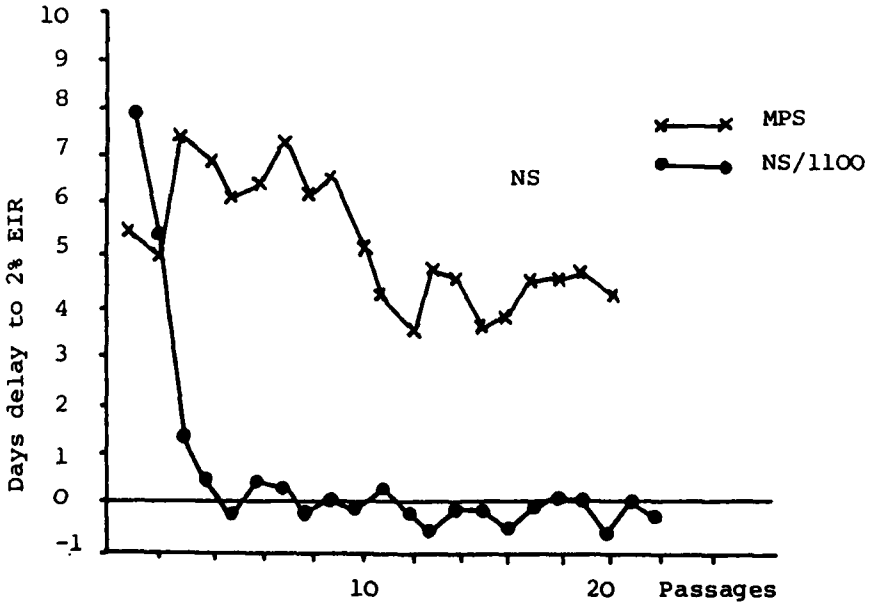

Fig. 1b. Development of resistance in chloroquine-resistant P.berghei (NS strain) to mefloquine alone (NS/1100) and to mefloquine administered together with Fansidar (MPS) using the relapse technique.

Plate 1. Effect of WR 194965 on blood stage of P.berghei (N strain) 3 hours post treatment with a single dose of 10 mg/kg sc. (x 52000)

Note swelling of digestive vacuoles and release of pigment into cytoplasm.

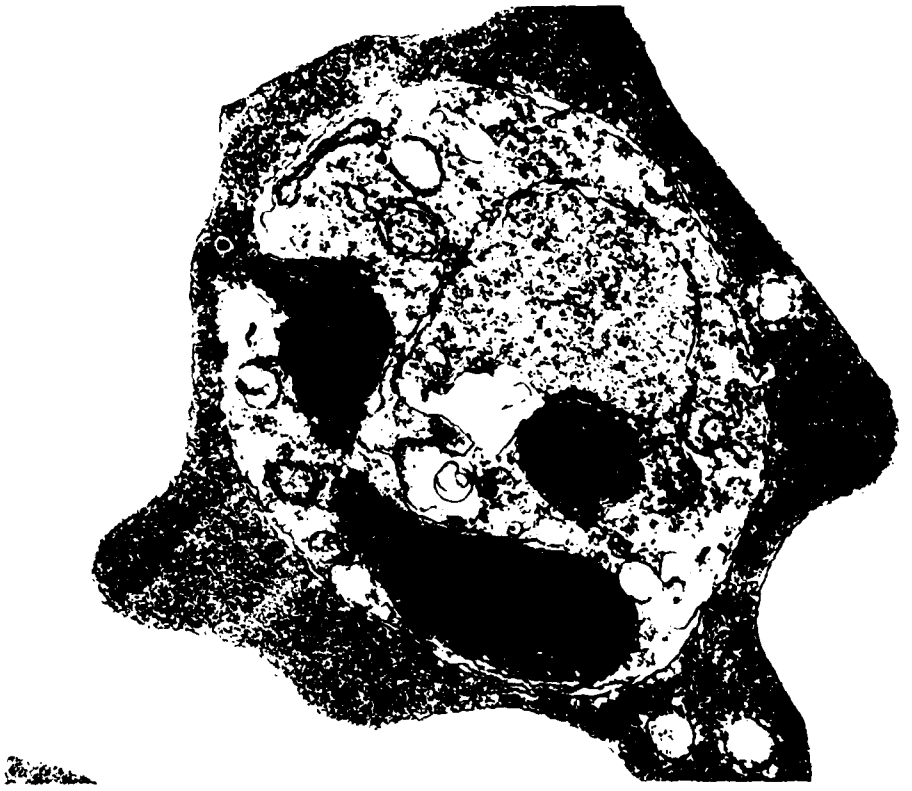

Plate 2. Effect of WR228258 on blood stage of *P.berghei* (N strain) 1 hour after treatment with a single dose of 10 mg/kg sc (x 26000)

Note nuclear blebbing and generalised membrane damage at 1 hour.

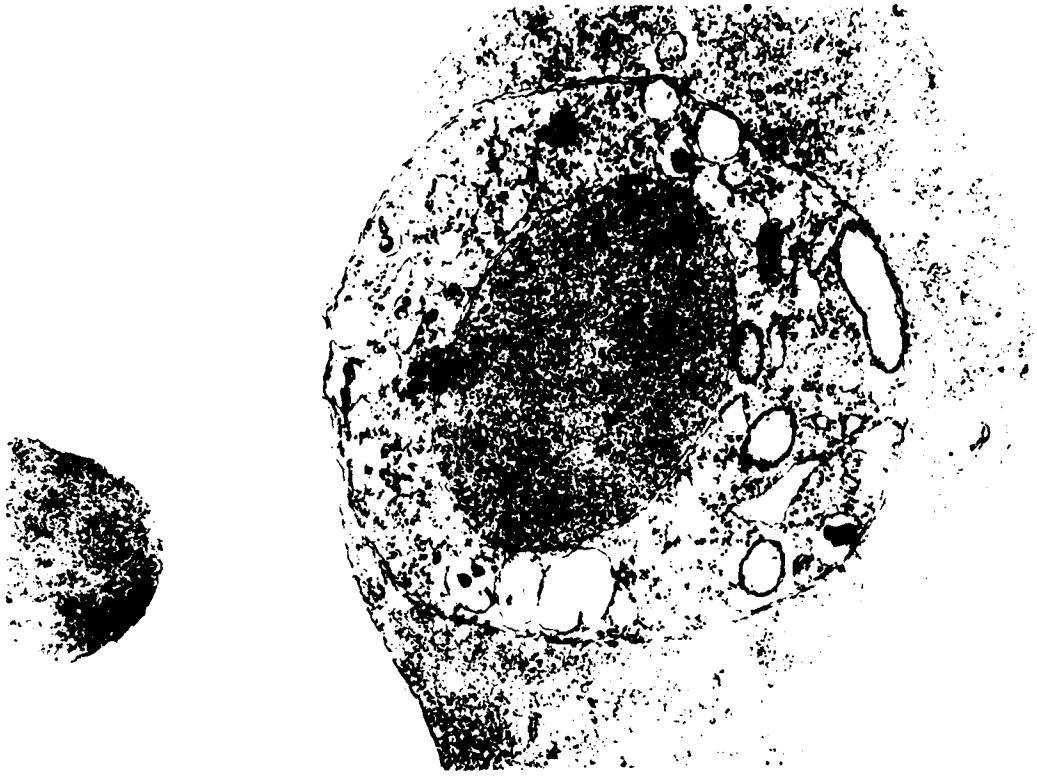

Plate 3. Effect of WR 225448 on blood stage of P.berghei (N strain) 24 hours after treatment with a single dose of 10 mg/kg sc. (x 26000)

Note the marked proliferation of mitochondria

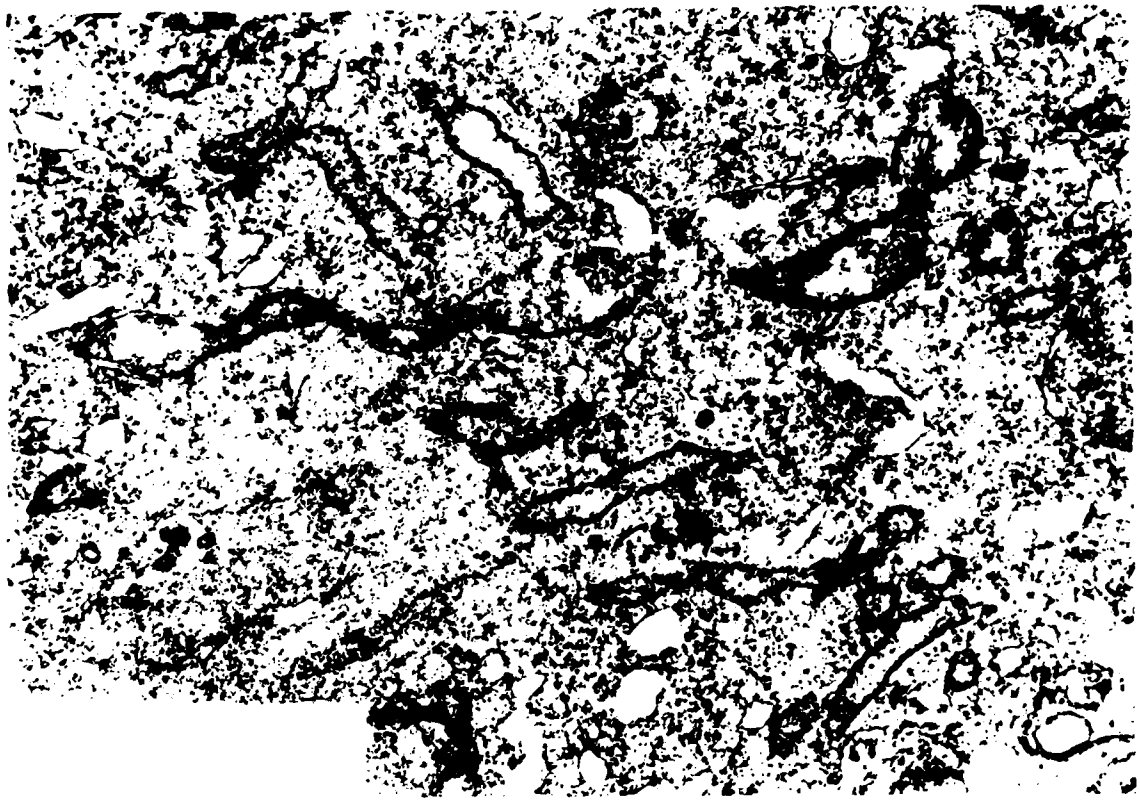

Plate 4. 45 hour exoerythrocytic schizont of P.y. nigeriensis in rat liver showing the effect of a single sc. dose of 50 mg/kg primaquine administered 3 hours after infection. (x 26000)

Note the thickening and darkening of mitochondrial membranes and early pathology of these organelles

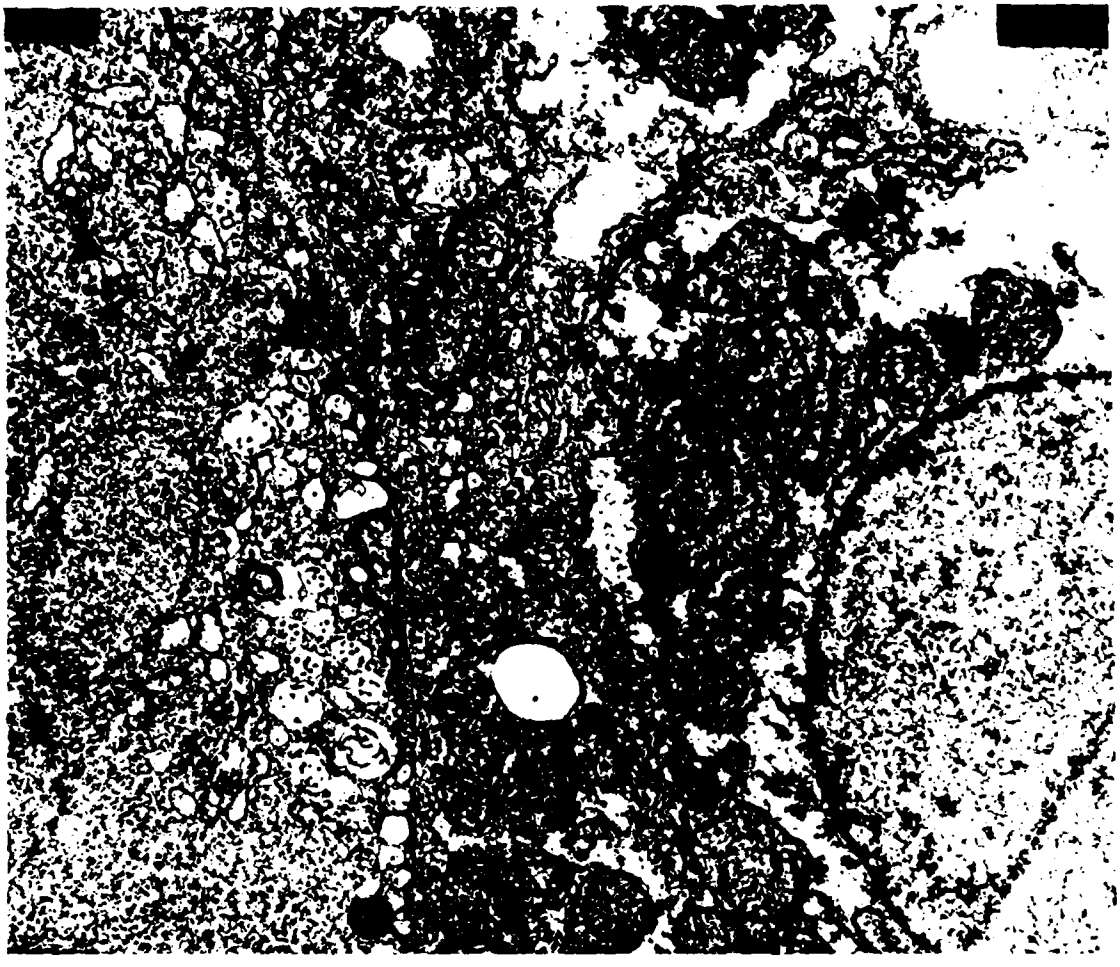

Plate 5. 45 hour exoerythrocytic schizont of P.y.nigeriensis showing the effect of a single sc. dose of mg/kg WR 225448.

Note that the "enzyme" particles are no longer breaking out of the parasite membrane to act on host cell. The drug has apparently stopped completely this normal parasite activity. The outer parasite membrane is here straight and without bursting "enzyme" vacuoles.